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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,429	11/04/1999	SHAUN A. KIRKPATRICK	11160	2571

7590 07/29/2003

LEOPOLD PRESSER
SCULLY SCOTT MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER
KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
1636	22

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/433,429	KIRKPATRICK, SHAUN A.	
	Examin r	Art Unit	
	Konstantina Katcheves	1636	

-- Th MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 25-31* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-20 and 23-31 are pending in the present application. Claims 18-20 and 25-31 are currently under consideration.

In view of the Appeal Brief filed on 12 May 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Response to Arguments

Claims 18-20, 27 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gorman in view of Builder et al. (U.S. Patent 5,663,304), Meulien (U.S. Patent 5,521,070), Ritter et al. (1991. Journal of Biological Chemistry. 266:1043-1047) and Ciotti et al. (1996. Biochemistry 35:10119-10124) for the reasons of record set forth in the Office Action mailed 22 March 2001. The rejection of claims 25-26 and 29-31 over 35 U.S.C. 103(a) have been withdrawn.

Applicant cites *In re Vaeck*, 947 F2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) that there is no suggestion is implicit or explicit in the prior art to carry out the claimed invention. Contrary to Applicant's assertion motivation to combine the instant references does indeed exist. Applicant argues that there is no motivation in the prior art to use Sertoli cells to produce a polypeptide of interest such as, Factor VIII, Factor IX or B-UGT. Gorman teaches in the working examples, effective production of biological factors in Sertoli cells by transforming these cells with constructs comprising a gene encoding a polypeptide of interest. Moreover, Gorman explicitly discloses a number of cell lines commonly used for the expression of desired proteins. Gorman states that "preferred suitable host cells for expressing the vectors of the instant invention encoding the desired heterologous proteins in higher eukaryotes include: . . . mouse sertoli cells. . .." Gorman clearly recognized the usefulness of sertoli cells as a host cell for a vector encoding a protein of interest. Thus, contrary to Applicant's assertion one of skill in the art would have been motivate and would have reasonably expected that a vector comprising the proteins

As previously discussed, Builder et al. teach expression of DNA encoding a desired polypeptide. Builder et al. teach that suitable host cells appropriate for the expression of the DNA encoding the desired polypeptide include useful mammalian host cells lines such as mouse sertoli cells (TM4) (column 14, lines 3-65). Builder et al. also teach that polypeptides of interest include molecules such as factor VIIIC and factor IX, among many others (see column 8, lines 24-65, especially lines 45-46, and column 9, lines1-9). Meulien et al. teach that in the sequence coding for Factor IX, there is a signal sequence encoded in the cDNA (see column 1, lines 62-67). Meulien et al. do not teach Sertoli cells. Ritter et al. teach the cloning of cDNAs for two

bilirubin UDP-glucuronosyltransferases (B-UGT in the instant claims). These have signal peptides (see abstract). Ritter et al. also teaches diseases resulting from loss of bilirubin glucuronidating activity, such as Crigler-Naijar syndrome (see page 1043, right column). Ciotti et al. also teach vectors comprising bilirubin UDPglucuronosyltransferase and mutants thereof, and the study of the activity of the proteins expressed from the vectors in COS cells. See abstract, page 10120, and the Discussion section.

Applicant has asserted that Muelin et al., Ritter et al. and Ciotti et al. do not teach Sertoli cells and thus do not teach vectors which function in Sertoli cells. Gorman et al. and Builder et al. teach Sertoli cells. These references are cited for what they teach together not individually. The suggestion of Gorman taken in light of Builder, which specifically discloses Factor IX as a polypeptide of interest and Sertoli cells as useful mammalian cells, the ordinary skilled artisan would have been motivated to produce biological factors of interest in Sertoli cells. One would have also been motivated to use a promoter that functioned in the cells, as well as 3' termination signals, so that the polypeptides would be expressed. Since many biological factors, such as Factor VIII, Factor IX, and B-UGT, have signal sequences, which are upstream of the coding region of the rest of the protein and downstream of any promoter, there would have been motivation to include those signal sequences, encoding signal peptides, in vectors for expressing the biological factors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 26 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The nature of the invention and the breadth of the claims:

Applicant's invention is broadly drawn to Sertoli cells comprising a vector which encodes a biological factor, wherein said Sertoli cells create an immunologically privileged site *in vivo*. The invention involves two complex functions. First, the invention is a form of gene

therapy wherein a sertoli cell transfected *ex vivo* with a construct comprising a heterologous protein is used to supplement a deficiency in a subject *in vivo*. Additionally, this invention involves the creation of an immunologically privileged site such that the transplanted cells are not affected by the subject's immunological responses.

State of the art and unpredictability of the art:

Although much has been advanced in the gene therapy field, much work remains in the area to overcome various obstacles inherent in the practice of gene therapy and to overcome the resulting unpredictability of the art. There are three basic categories of somatic cell gene therapy: *ex vivo*, where the cells are removed from the body of the subject incubated with a vector and returned to the subject; *in situ*, where the vector is place directly into the affected tissue; and *in vivo*, where the vector may be injected into the blood stream. See Anderson (Nature Vol.392 1998) Box 1. The present invention is drawn to the first of these types of gene therapy. According to Verma et al. (Nature Vol. 389 1997), "the lack of efficient delivery systems, lack of sustained expression, and host immune reactions remain formidable challenges" and the "transient expression of the transgene is a conceptual hurdle that needs to be addressed. See Verma et al., page 239. See also Anderson page 25, column 1 and Palu page 9 (J. of Biotech. Vol.68 1999).

Verma et al. exemplifies the problems of *ex vivo* gene therapy. A somatic cell was transfected *ex vivo* with a construct comprising the gene for factor IX. However, within days of transplanting the cells back to the subject expression of facto IX is shut off even in nude mice, which is not due to cell loss or gene deletion. The problems associated with establishing sustained transgene expression in *ex vivo* gene therapy include finding the right enhancer-

promoter combination, efficiency of transplantation and host immune response. See Verma page 240. Thus, absent evidence to the contrary, the expression of the biological factor from the transformed sertoli cells of the present would be unpredictable *in vivo* would be unpredictable based on the state of the art at the time the invention was made.

Another aspect of the present invention that adds complexity to the invention and increases the unpredictability in the art to practice the claimed invention is the claim that the transformed Sertoli cells create an immunologically privileged site *in vivo*. The testis is known as an immunologically privileged site. However, Sundstrom et al. (J. of Reproductive Immunology Vol.42 no.2 1999) state that little is known about the formation of immune responses in the testis. See abstract. Given this statement, it is difficult to extrapolate that the contribution that Sertoli cells have in making the testis an immunologically privileged site could translate to creating an immunolgically privileged site anywhere in the body of a subject.

Guidance provided in the specification and absence of working examples:

The specification asserts that the Sertoli cells of the claims comprise vectors encoding biological factors such as factor VIII and IX and B-UGT such that an immunologically privileged site is formed in vivo and the cells express a biological factor deficient in the subject. Applicant has, however, failed to substantiate or support these assertions to overcome the state of the art. The specification fails to provide adequate working examples showing that these cells can be used as asserted. Applicant's examples are prophetic and fail to provide adequate guidance to those of skill in the art to make and use the invention. For instance, Example 1 teaches Sertoli cells that can be transfected with a construct comprising β-gal; Example 2 teaches these cells can be transfected into a rat under the kidney sub-capsular space; Example 3 teach

Sertoli cells that may be transfected with a vector comprising an alkaline phosphatase gene; Example 4 discusses porcine cells transformed with the vector of Example 1; Example 5 discusses that Sertoli cells altered to express factor IX may be transplanted into rats; and Example 6 discusses that Sertoli cells comprising B-UGT may be transplanted under the kidney capsule. These examples instruct that one may assess the activity of the transplanted Sertoli cells over various time periods. However, nowhere in the specification is there any data showing that either the biological factor is expressed in the subject or that the Sertoli cells create immunologically privileged sites *in vivo*. Moreover, one should note that the kidney sub-capsular space under which Applicant teaches that transfected Sertoli cells may be implanted, as in Example 6 in the specification, is itself considered an immunologically privileged site. Thus, calling into question whether it is in fact the Sertoli cells of the claimed invention that can even create an immunologically privileged site. See Cole et al. (J. of Materials Science: Materials in Medicine Vol.4 no5 pp437-442), abstract. (The full text of Cole et al. is currently unavailable, but has been ordered. The article will be forwarded to Applicant as soon as practicable)

Quantity of Experimentation Necessary:

Given the state of the art, the nature and breadth of the invention and the lack or working examples as discussed above, one of skill in the art would be required to engage in an undue amount of experimentation to determine how to make and use a Sertoli cell to achieve sustained expression of a biological factor and to create an immunologically privileged site *in vivo*. Without further evidence, Applicant has not overcome the state of the art and the unpredictability

of the art. Thus, Applicant is not enabled for Sertoli cells comprising a vector which encodes a biological factor, wherein said Sertoli cells create an immunologically privileged site *in vivo*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
July 25, 2003

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